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The Report of a Case of Idiopathic Congenital (and Probably Familial) Methemoglobinemia. COMDR. ASHTON GRAYBIEL (M.C.) U.S.N.R., LT. J. L. LILIENTHAL, JR. (M.C.), U.S.N.R., AND LT. RICHARD L. RILEY (M.C.), U.S.N.R. 155

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THE REPORT OF A CASE OF IDIOPATHIC CONGENITAL (AND PROBABLY FAMILIAL) METHEMOGLOBINEMIA[1, 2]

COMDR. ASHTON GRAYBIEL (M.C.) U.S.N.R., LT. J. L. LILIENTHAL, JR. (M.C.), U.S.N.R., AND LT. RICHARD L. RILEY (M.C.), U.S.N.R.

The following description of a case of congenital methemoglobinemia is of interest partly because of the rarity of this disorder but chiefly because of the instruction it affords with regard to certain physiological and pathological mechanisms.

N. L., a young man aged 19 years, of Irish and English descent, was first examined by us November 5, 1942. He was "blue" at birth and has remained so. During infancy and early childhood he was in poor health, although never seriously ill. His attendance at school was irregular, studying usually caused headache, and he had difficulty with the lessons. In playing with other boys he was limited by fatigue and shortness of breath. At the age of 17, having completed the 7th grade, he left school and went to work, driving a small truck and doing other light work without complaint. He continued at this job for nearly two years and then obtained his present position as a gasoline station attendant. Except for feeding problems in infancy and early childhood there was no history of chronic constipation or of gastro-intestinal illness. His diet, generally, was adequate and included citrus fruits and other foods containing a relatively large amount of ascorbic acid. He had never taken any drugs which are known to cause cyanosis or pigmentation.

The family states that a cousin of the patient was also "blue" at birth and remained so till his death at the age of 14.

Physical examination revealed a tall, poorly nourished, cyanotic young man. The ears, tongue, lips and especially the gingival margins of the gums showed intense cyanosis. The nail beds were blue in color but there was no clubbing of the fingers or toes. The scleral vessels were abnormally prominent and dark blue in color. The retinal arteries and veins appeared almost black. His respirations were normal. The heart was found not to be enlarged and the rhythm was regular. A systolic murmur of slight intensity was heard over the base of the heart. The blood pressure was 130 systolic and 100 diastolic. The lungs were clear, the liver and spleen could not be felt and there was no demonstrable edema.

An examination of the blood was reported to reveal no abnormality in the

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[2] The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

number or morphology of the leukocytes; the erythrocyte count was 5.8 million per cmm., and the hemoglobin concentration was 16.0 gms. per 100 cc. Radiologic examination of the heart and lungs disclosed no abnormalities except "slight right ventricular hypertrophy and the aortic knob is placed higher than usual." The electrocardiogram was normal except for right axis deviation index + 19 and angle + 117°. Radiologic examination of the long bones revealed normal epiphysial development.

On June 7, 1944 a sample of arterial blood was obtained for blood gas analysis (1). The blood was chocolate-colored. Parenthetically,

FIG. 1. CASE N. L.

it may be pointed out here that if, at the time of the original examination, the chocolate color of the blood had been reported, the presence of an abnormal blood pigment might have been suspected at that time. The oxyhemoglobin *content* of the sample of blood was found to be 13.2 vol. per cent. This low value was consistent with the degree of cyanosis shown by the patient. However, the oxyhemoglobin *capacity* of the same sample of blood was only 15.3 vol. per cent, and the brown color of the blood remained unchanged after equilibration with air. A hemoglobin concentration of 16.0 gms. per 100 cc.

as determined in this patient corresponds to an oxyhemoglobin capacity of 21.3 vols. per cent. Since the determined oxyhemoglobin capacity was only 15.3 vols. per cent it was evident that normal hemoglobin formed only a portion of the blood pigment present. The normal hemoglobin was 86 per cent saturated with oxygen, a degree of saturation too high to account for the extreme cyanosis. The conclusion was inescapable, therefore, that a large amount of some abnormal pigment was present.

A method for the quantitative estimation of methemoglobin was suggested by Dr. Robert Darling of the Harvard Fatigue Laboratory (2). The method is based upon two facts, first, that normal hemoglobin combines with carbon monoxide while methemoglobin does not, and second that sodium hydrosulfite ($Na_2S_2O_4$) reduces methemoglobin to reduced hemoglobin, which can then combine with carbon monoxide. The difference in carbon monoxide combining capacities between hydrosulfite-treated and untreated blood provides a measure of methemoglobin content. Carbon monoxide capacities of the venous blood of the patient determined by this method were 17.6 vol. per cent before, and 28.4 vol. per cent after reduction with sodium hydrosulfite. This indicated that 38 per cent (8.1 gms.) of the circulating blood pigment could not combine with carbon monoxide and was, presumably, methemoglobin. This presumption was confirmed by spectroscopic analysis of the blood through the kindness of Senior Surgeon Paul A. Neal and Dr. Bernard L. Horecker of the U. S. Public Health Service. The hemoglobin concentration was found by them to be 18.7 gms. per 100 cc. of which methemoglobin contributed 8.5 gms. (46 per cent). No significant quantities of sulfhemoglobin were present.

They also made the interesting observation that the methemoglobin level remained practically unchanged when the blood was kept at room temperature for 24 hours; by contrast, the methemoglobin in the blood of patients suffering from toxic methemoglobinemia will be largely reduced to normal hemoglobin under the same conditions. Neal points out (3) that this finding alone is fairly conclusive evidence that the patient under observation is suffering from familial idiopathic methemoglobinemia. Lian *et al.* (4) observed similar stability of the methemoglobin in the two cases they described.

Methemoglobin is changed to reduced hemoglobin by a variety of oxidizing and reducing agents. Among these are two substances which can be administered safely to man, namely, methylene blue and ascorbic acid. In view of two recent reports which described the favorable effects of ascorbic acid in the treatment of idiopathic methemoglobinemia (4, 5), our patient was given 100 mgm. of ascorbic acid and 0.6 gms. of sodium bicarbonate three times daily by mouth beginning on July 27. The sodium bicarbonate was administered because alkalinization has been shown to decrease the urinary excretion of ascorbic acid and thus decrease the rate at which ascorbic acid disappears from the blood (5).

Four days later the patient's sclerae appeared to be less injected, and the lips slightly less cyanotic; the methemoglobin percentage, determined by the carbon monoxide method, had fallen to 25 (6.4 gms). After 14 days of treatment the methemoglobin percentage had fallen to 11 (2.5 gms). The daily dose of both ascorbic acid and sodium bicarbonate was doubled on the 19th day and two weeks later the percentage of methemoglobin was 8 (1.7 gms). Slight cyanosis was still present but the change in appearance of the patient was striking. Thus, after 19 days of treatment the methemoglobin concentration had fallen from 8.1 gms to 1.7 gms and the normal hemoglobin had increased from 13.1 gms to 15.8 gms.

In spite of these changes the patient stated that he felt very little different after treatment. The impression was gained however that he had become irritable. Prior to beginning treatment he was pleasant-tempered, appreciative of any medical attention and unfailingly cooperative. Following treatment he became somewhat irritable and not always cooperative. He seemed to take no pleasure in the fact that he had become nearly normal in appearance.

In order to estimate the effect on a variety of functions of the increase in the oxygen carrying capacity of the blood several observations were made before treatment and after the level of methemoglobin had fallen to the 10 per cent level.

a) The following battery of psychological tests were conducted through the courtesy of Miss Mary E. Nickinson: the Wechsler-Bellevue and revised Stanford-Binet (forms L and M) intelligence tests, the Otis Higher Examination (forms A and C), the Multiple

Choice Rorschach Test and the Psychosomatic Inventory. The test scores all indicated below average intelligence and none of them showed any improvement after treatment, including those items in the examinations which test the attention, memory, visual motor perception and coordination.

b) Dark adaptation, a visual function which is measurably impaired by mild degrees of anoxia, was tested by Lieut. W. B. Clark, H (S), U.S.N.R. No change in the rate of dark adaptation was detected during treatment.

c) Examination of the cardiovascular system revealed great reduction in the intensity of cyanosis. The scleral vessels were no longer dilated. The lips and tongue became almost normal in appearance but the nail beds still showed moderate cyanosis. When the hands were warmed the cyanosis of the fingers virtually disappeared. There was no change in the average resting heart rate or in the blood pressure. The murmur heard over the base of the heart was unchanged. Fluoroscopic examination on August 28 revealed a slight but definite decrease in the size of the right ventricle when compared with the two examinations made before treatment was begun. The aortic arch was noted again to be in a high position. An electrocardiogram taken October 28 no longer showed right axis deviation (axis 90°) but was unchanged in other respects.

d) Exercise tolerance was determined by means of the step test which has been shown to yield a reliable measurement of the fitness to do hard work (6). Shortly before treatment was begun the test score was 28, indicating poor fitness for hard work. Two months later the score was 52; a low average score. This increase of 85 per cent represents a marked improvement in the capacity for hard physical work.

DISCUSSION

Minute amounts of methemoglobin are found (7) in the blood of healthy persons. Pathological methemoglobinemia is most commonly observed in man as the result of the action of certain drugs or of bacterial infections. It is also observed, and our case is an example, as the result of a metabolic disturbance (8). Two characteristics of this idiopathic form are (1) the methemoglobin is found only in the

red blood cells (none is found in the plasma) and (2) after exposure to air, the methemoglobin does not readily revert to hemoglobin as does methemoglobin of toxic origin (5). In some of the cases of idiopathic methemoglobinemia the familial nature of the metabolic defect has been shown; and Lian and his associates (4) have provided evidence that this defect is transmitted as a dominant Mendelian characteristic.

Methemoglobin differs from hemoglobin in that the iron is in the ferric rather than the ferrous state and has formed a relatively stable compound. As a result methemoglobin is physiologically inert with respect to the transport of oxygen. In this regard it resembles carboxyhemoglobin.

Although the cyanosis of methemoglobinemia resembles the cyanosis of anoxemia, the pathologic physiology of the two conditions may be sharply contrasted. In methemoglobinemia the oxygen tension of the arterial blood is presumably normal because the blood equilibrates with normal alveolar air in the lungs. In anoxemia, on the other hand, the oxygen tension in the arterial blood is low, due either to a shunt, which partially by-passes the alveoli, or to an abnormally low alveolar oxygen tension. If the *amount* of oxygen carried by the arterial blood should happen to be the same in the two conditions, the degree of tissue anoxia would be, nevertheless, more severe in the case of anoxemia because the *pressure* of oxygen would be lower. The patient with anoxemia is therefore much more handicapped functionally than the patient with a comparable degree of cyanosis as a result of methemoglobinemia.

The cyanosis of idiopathic methemoglobinemia has been described predominately "blue" in color and lacking the "wine-color" tint observed in cyanosis due to anoxemia. An opportunity to compare the cyanosis in this case with the cyanosis of anoxemia was offered by the studies on experimental anoxia which were in progress when this patient was studied. The impression was gained that moderate degrees of cyanosis due to methemoglobinemia could not be distinguished clinically from those due to anoxemia.

The cardiac findings were interesting and somewhat misleading. The changes which occurred after treatment suggest that the slight right ventricular enlargement and right axis deviation were associated

with the chronic methemoglobinemia. The strain imposed on the heart as a result of the decreased oxygen capacity of the blood and the distortion of the normal oxyhemoglobin dissociation curve offers a reasonable explanation for the cardiac changes. It is not surprising, therefore, that most of the patients with methemoglobinemia from birth have been considered initially to have congenital heart disease. The absence of marked structural changes in the heart, the disproportion between the relatively good exercise tolerance and the intense cyanosis and the absence of clubbing are important features in the differential diagnosis. Methemoglobinemia may be suspected in patients with intense cyanosis whose blood is chocolate-colored and fails to become crimson on exposure to air. The presence of methemoglobin can be established by spectroscopic examination of the blood.

It is altogether likely that some patients showing cyanosis, who are now regarded as having congenital heart disease, have, in fact, idiopathic methemoglobinemia.

The result of treatment with ascorbic acid and sodium bicarbonate was little short of dramatic, with respect to the decrease in cyanosis and in the concentration of methemoglobin. The exact mechanism of the effect of ascorbic acid is not known; it seems reasonable to assume that the increased concentration of ascorbic acid in the blood acts as a non-specific biological reducing agent rather than as a supplement to any primary deficiency of ascorbic acid. Ascorbic acid reduces methemoglobin to normal functioning hemoglobin, and the speed of the reaction *in vivo* suggests that this occurs within the erythrocyte. The site of the metabolic defect which permits the production of methemoglobin is unknown.

SUMMARY

A case of congenital idiopathic methemoglobinemia has been described. Evidence is presented to suggest the familial nature of the disorder. The striking clinical feature was the intense cyanosis which was out of proportion to the other clinical findings. Attention is drawn to the features which are common to both idiopathic methemoglobinemia and congenital heart disease with cyanosis. Simple inspection of a drop of the patient's blood may provide the differential

clue. It is altogether likely that some cyanotic patients now regarded as having congenital heart disease have, in fact, methemoglobinemia. Ascorbic acid, a biological reducing substance, is capable of converting methemoglobin to normal hemoblobin *in vivo*.

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REPORT OF A CASE OF ACUTE INTERSTITIAL FIBROSIS OF THE LUNGS[1]

HOWARD EDER, M.D.[2] CLINTON VAN ZANDT HAWN, M.D.[3] AND GEORGE THORN, M.D.

Hamman and Rich (1) have recently reported an unusual group of cases of pulmonary disease. These presented the clinical features of marked dyspnea and cyanosis with subsequent heart failure due to dilatation and hypertrophy of the right ventricle: at autopsy a peculiar interstitial fibrosis of the lungs was found.

Shortly before the publication of the report mentioned, we had occasion to observe a puzzling case of pulmonary disease on the Medical wards of this Hospital. After autopsy it became apparent that this case had many of the features of those described in the publication which appeared at that time. Accordingly, we report an additional case of "Acute Diffuse Interstitial Fibrosis of the Lungs."

M 66226—V. C., a 47 year old Italian-born waiter was admitted to the Medical Service of the Peter Bent Brigham Hospital complaining of cough and shortness of breath. He had been in good health until 4 months before admission when he noticed slight dyspnea on exertion. Three and one-half months before admission he developed a sore throat and a non-productive cough; the former subsided but the latter persisted. The exertional dyspnea increased in severity. The patient was forced to give up his work. Two months before admission he noted marked dyspnea on awakening. He experienced attacks of severe dull pain over the xiphoid. These were induced by exertion, did not radiate, and subsided after a few minutes of inactivity. He received digitalis from his family physician with no improvement. His wife stated that during the period of his illness he was "nervous", and that he perspired more than usual and lost 15 pounds.

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[2] Research Fellow in Medicine.

[3] Junior Fellow, Society of Fellows, Harvard University, Instructor in Pathology, Harvard Medical School, Junior Associate in Pathology, the Peter Bent Brigham Hospital.

The patient was born in Italy where he remained as a farmer until 1921 when he came to Boston. He worked as a waiter since. He had gonorrhea in 1917.

Physical Examination—Temperature 98.4°F. Pulse 128 per min. Blood Pressure 124/82 mm. Hg.

He was a thin, somewhat apprehensive, middle-aged man lying quietly in bed but quite dyspneic whether lying flat or sitting. He had a dry non-productive cough. His skin was warm and his palms were moist. There were many elevated petechiae over the chest and abdomen; these measured on the average 1 mm. in diameter. They did not blanch on pressure. His nail beds and lips were slightly cyanotic. The finger-tips were definitely clubbed, and there was a slight tremor of the outstretched hands. There was no enlargement of the peripheral lymph nodes. The pupils were equal and reacted to light. There was a slight stare but no lid-lag or failure of convergence. The thyroid was not enlarged. The neck veins were not engorged. The trachea was in the mid-line and the lungs were normal to percussion. A few transient râles were heard in the right axilla. On percussion the heart was slightly enlarged to the left. The rhythm was regular. The sounds were hyper-active and a loud protodiastolic gallop was heard at the apex. The pulmonic second sound was louder than the aortic. The abdomen was relaxed; no organs or masses were palpated. The genitalia were normal. There was no tenderness of the calves and no peripheral edema. Pulsations of the dorsalis pedis artery were palpated at each ankle.

Laboratory Data: Serological test for syphilis was negative. Highest recorded urine concentration was 1.010. Urine at no time contained protein, sugar, or acetone. The sediment contained occasional red and white blood cells; there were no casts. Red blood cell count was 4.5 million: hemoglobin, 16.5 gm. %, hematocrit, 52%. Sedimentation rate was 26 mm. per hour. White blood cell count on admission was 11,300 with 77% neutrophiles. Blood urea nitrogen was 27 mg. %; fasting blood sugar was 110 mg. %. The stools appeared normal and contained no occult blood. Culture of sputum grew out moderate numbers of *Streptococcus beta hemolyticus*, *B. coli*, and *Staphylococcus albus*. Blood culture gave no growth. Vital capacity on admission was 1700 cc. Circulation time (arm to tongue

with Decholin) was 15 seconds. Venous pressure (method of Burwell) was 143 mm. H_2O. First strength tuberculin was negative. Prothrombin time, bleeding time, and clotting time were normal. Lumbar puncture showed initial pressure of 210 mm. H_2O with normal dynamics. The fluid was clear and contained no cells. X-ray films of the chest showed extensive fine mottling of both lungs most marked in the upper lobes, findings suggestive of miliary tuberculosis; the heart was enlarged both to the right and to the left and measured 30% above the normal for the appropriate height-weight ratio. (Figure 3.) Electrocardiogram on the 3rd hospital day showed right axis deviation with a sinus tachycardia (rate 120 per min.).

Hospital Course: During his first 3 days in the Hospital the patient did not appear acutely ill. His temperature gradually rose from normal on admission to 102°F. at the end of the third day. Respirations ranged between 30 and 50 per min. Pulse remained at 120 per min. On the fourth day there was a sudden change. He complained of excruciating pain in both legs. He appeared extremely ill. He had marked cyanosis and severe air hunger with a respiratory rate of 60 per min. The blood-pressure dropped to 90/55 mm. Hg, but the pulse rate did not increase. Both legs became mottled and cool below the mid-calf. Femoral pulsations were diminished on both sides. No pulsations of the dorsalis pedis arteries could be felt. Many more petechiae appeared over the abdomen and anterior chest. Lungs remained unchanged to physical examination. The heart beats were forceful with accentuation of the protodiastolic gallop rhythm. The abdomen remained relaxed and peristalsis was present. White blood cell count rose to 25,000 with 95% neutrophiles. The electrocardiogram showed no change from the previous tracing. Plasma, morphine, oxygen, and papaverine were administered with moderate improvement in the patient's condition. Blood pressure rose to 110/70 mm. Hg. On the following day the right leg was cold below the knee but only the foot was cold on the left. Dyspnea remained marked: the respiratory rate was 55 per min. and there was extreme cyanosis. Oxygen administration afforded striking relief from the air hunger. Two days before death a pleural friction rub was heard in the right axilla. The marked dyspnea and cyanosis persisted and the patient died in respiratory failure 8 days after admission.

At autopsy both pleural cavities were found to be obliterated by moderately dense fibrous adhesions. The right lung weighed 1230 gm., and the left, 1090 gm. Crepitancy could be elicited only in the basal one-third of each lower lobe; elsewhere there was general consolidation. On sectioning, the surfaces presented the mosiac appearance of diffuse fibrosis with interspersed areas of emphysema as well as areas of pneumonic consolidation. The lungs essentially resembled

FIG. 1. RIGHT LUNG

There are diffuse macroscopic scars more prominent in the upper and middle lobes. Small patches of emphysema are seen at the apex. A portion of diaphragm is adherent to the visceral pleura.

each other. The interlacing bands of connective tissue were broader and denser in the upper lobes and in the upper two-thirds of the lower lobes. (Figure 1.) The macroscopic bronchioles were not dilated. The trachea and bronchi contained no purulent exudate evident in the gross. No thrombi were encountered in the larger pulmonary arteries or veins.

Microscopically there was striking and extensive interstitial fibrosis throughout both lungs. The connective tissue composing the mark-

edly thickened alveolar walls appeared relatively recently formed. Hyalinization of the bundles of collagen fibers was minimal. There were numerous dilated capillaries. The connective tissue was moderately cellular and in some few areas the fibroblasts could be seen still to be proliferating. Scattered mononuclear phagocytes, lymphoid cells and occasional polymorphonuclear leukocytes were encountered in the interstitial connective tissue. Eosinophiles were rare. Many of the alveoli contained exudate composed of moderate numbers of poly-

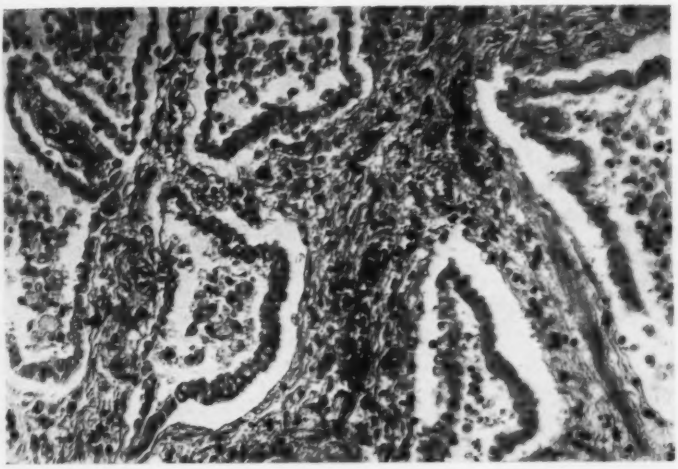

FIG. 2. Alveolar walls are greatly thickened by recently formed connective tissue and capillaries. The alveoli are lined by very prominent epithelium; some contain desquamated epithelial cell débris, mononuclear phagocytes and occasional polymorphonuclear leukocytes. Eosine and methylene blue stain, × 300.

morphonuclear leukocytes as well as mononuclear phagocytes, desquamated epithelial cells and cell débris. In some of these collections of exudate occasional intracellular and extracellular diplococci were found. They were positive in the Gram-stained sections. In some few alveoli there were small hemorrhages, recent in origin; rarely intra-alveolar hemorrhages and exudate could be found to be undergoing organization. There was generalized prominence of the alveolar epithelium. (Figure 2.) The bronchioles were relatively free from exudate. There was no bronchiectasis. Many of the small pul-

monary vessels showed moderate to marked obliterative fibrosis. Some of these were occluded by fibrin and platelet thrombi which appeared recent but not fresh. The pleural surfaces showed numerous

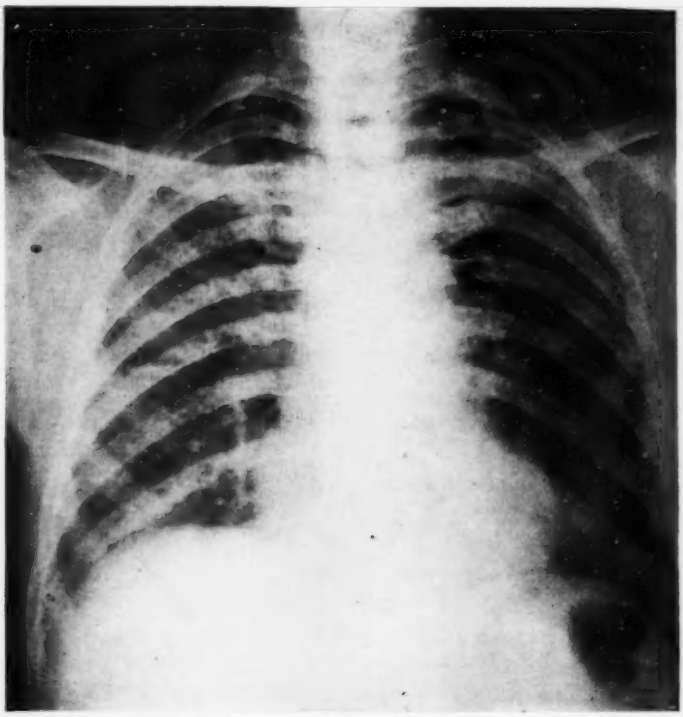

FIG. 3. X-RAY FILM OF THE CHEST

There is extensive fine mottling of both lungs, most marked in the upper lobes, with a fine granular appearance partly obscuring the individual nodules. Heart appears enlarged, both to the right and left, about 30% above average. Hilar shadows are thickened and irregular.

cellular fibrous adhesions. There was no evidence of tuberculosis. The tracheo-bronchial lymph nodes were enlarged; the sinuses contained moderate numbers of polymorphonuclear leukocytes and monocytes.

The heart weighed 310 gm. There were no pericardial adhesions. There was slight dilatation of the right ventricle and right atrium. The musculature of the right ventricle was appreciably hypertrophied; it measured 0.7 cm. in thickness on the average. The valves showed no lesions and on microscopic study the heart was essentially normal.

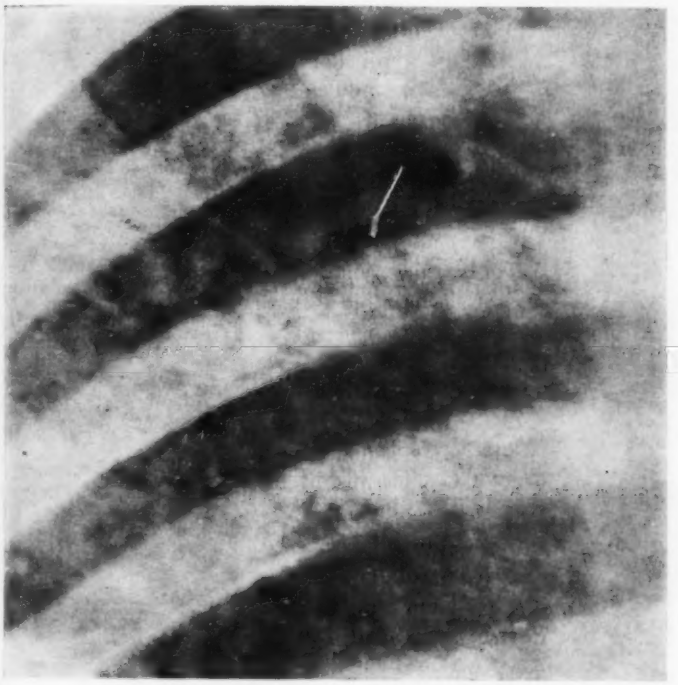

FIG. 4. ENLARGED DETAIL OF X-RAY FILM OF CHEST

There was only slight sclerosis of the aorta but this vessel contained extensive friable ante-mortem thrombus overlying and entering several of the intercostal arteries. This thrombus was lightly adherent to the intimal surfaces. The right iliac artery was occluded by adherent thrombus; a free thrombus partially occluded the left iliac artery. No thrombus was found above the level of the intercostal arteries. No thrombi were found in the heart or in the larger pulmonary veins or

their macroscopic tributaries. The inferior and superior venae cavae and their major tributaries were free from thrombi.

Other pertinent findings included recent and fresh infarcts in both kidneys, focal necrosis and focal fibrosis of the pancreas and a generalized papular rash over the neck and trunk. Microscopic study of the skin lesions showed non-specific petechial hemorrhages and focal accumulations of monoclear phagocytes at the tips of the papillae in the dermis. The liver weighed 1050 gm.

Cultures of the upper lobes of the lungs taken at autopsy grew out only *Streptococcus alpha hemolyticus*.

DISCUSSION

The resemblance of the case presented to those described by Hamman and Rich is striking. This patient showed marked evidence of advanced pulmonary disease as did the 4 cases previously reported. The presenting symptoms were also shortness of breath and cough. Dyspnea was moderate at first but progressively became very marked with associated rise in the respiratory rate and the development of extreme cyanosis. Administration of oxygen gave considerable relief. It is interesting to note that despite the extensive fibrosis of the lungs the physical examination of the lungs yielded only minimal evidence of the disease. In the case here presented, as in 2 of the 4 cases previously described, only scattered râles were heard on first examination. Later this patient developed a pleural friction rub; this sign appeared in 2 of the previous cases. Clubbing of the fingers was unique to this case. The X-ray appearance of the lungs suggested miliary tuberculosis in this patient as in 2 of the previous cases.

The cardiac findings of the case presented were those of chronic *cor pulmonale*. The heart was definitely enlarged and there was a loud gallop rhythm. A gallop rhythm was described in 2 of the earlier cases. The electrocardiogram showed right axis deviation; this was noted in 1 of the other cases. At no time was there evidence of cardiac decompensation. There was no edema; the liver was not enlarged; the venous pressure and circulation time were normal. The total duration of the disease appears to have been about 17 weeks, which is well within the range of 4–24 weeks of the series.

The autopsy findings in the case presented included many of the

pathological peculiarities of the condition described by Hamman and Rich. Most outstanding was the marked diffuse interstitial proliferation of fibrous tissue throughout all lobes of both lungs. The progressive character of this was evidenced by the different stages in the fibrosis of various portions of the lungs. This still-active formation of interstitial connective tissue was present in 3 of the previously reported cases. The proliferation and prominence of the lining alveolar epithelial cells seemed identical with that described or illustrated in association with areas of more advanced fibrosis in all of the previously described cases. Apart from focal areas of terminal broncho-pneumonia there were no stainable bacteria in the pulmonary tissue and there was no residuum of the type of inflammation usually produced by pyogenic bacteria. These negative findings characterized all of the previously reported cases. There was slight to moderate hypertrophy of the right ventricular musculature in all of the previous cases and in the case presented.

There were a few points of difference. The formation of a hyaline membrane lining the alveoli was not conspicuous here nor were there striking numbers of eosinophiles in the interstitial connective tissue. Necrosis of alveolar and bronchial epithelium was not as prominent as in the former cases.

There are certain features of the case under discussion which have not been previously described, although the underlying process seems identical. The development of peripheral emboli, thrombi, and infarcts may be accounted for by propagation of thrombi from the small pulmonary veins. The infarcts in the kidneys and the focal necrosis and fibrosis of the pancreas are thus explained. Microscopic cutaneous emboli might similarly account for the development of the skin petechiae. The etiology of the underlying pulmonary disease remains obscure.

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BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

Fundamentals of Internal Medicine. Second Edition. By WALLACE MASON YATER. 1169 pp. Price $10.00. D. Appleton-Century Company, 1944.

The second edition of this textbook of internal medicine succeeds admirably in fulfilling its stated purpose of providing instruction for students, practitioners and members of the Armed Forces. Currently important items of military medicine have been added; therapeutic methods have been brought up to date; several new features are supplied. Among the latter a particularly valuable section discusses in commentary style, quotations from "Principles of Medical Ethics" of the American Medical Association. Embodied therein are some of the delicate mechanical and moral problems facing a young practitioner. The book is legible, bold-faced type being freely used. It is replete with illustrations, mostly well reproduced, many of these taken from papers previously published by the author and testifying to the breadth of his personal experience.

A. B.

Escleroses Valvulares Calcificadas. By Doctor ROBERTO MENEZES DE OLIVEIRA. Published in 1943 by Tipografia do Patronato, Rua Real Grandeza, 248, Rio de Janeiro, Brazil.

In this monograph the author has presented the results of his study of one hundred patient with calcification of heart valves or their sustaining structures. He has co-related the clinical symptoms and signs arising from these.

The work is divided into five parts. The first contains a resume of the anatomy and histology of the cardiac valves and their sustaining structures.

The second is devoted to an anatomic pathologic study and discussion of the process of calcifications noted in the skeleton and cardiac valves of twenty-five autopsy cases.

The third part discloses the results of the pre and post mortem radiologic studies of calcifications observed in the cardiac valves and their sustaining structures in these twenty-five cases. It also includes a presentation and discussion of radiologic findings in one hundred cases of calcification of or near the valves.

The fourth part contains the study of theclinical observations made in the cases.

The fifth part contains a resume of the findings and a discussion of their significance.

The investigation, which was made on the Anatomic-Pathologic, the Radiologic and the Clinic services of the Peter Bent Brigham Hospital, is well documented and concisely written. It should be a good source of information for investigators interested in the subject.

L. M.

An Introduction to Pharmacology and Therapeutics (Seventh Edition). By J. A. GUNN. 268 pp. $2.25. Oxford University Press, London, 1944.

This splendid little book needs no introduction to many teachers and students of pharmacology. It was designed to give the beginner a brief survey of the more important drugs from the standpoint of their principal actions and uses. Naturally, in order to preserve clarity and brevity, controversial topics have been avoided largely, and there are no references to the original literature.

A comparison with the previous edition indicates that the slight increase in length of the present edition is due primarily to addition or revision of sections on non-volatile anesthetics, autonomic drugs, vitamins, sulfonamides, and other chemotherapeutic agents. It is a bit surprising that nikethamide and metrazol were not classed among the central nervous system stimulants, and that no mention was made of mapharsen and penicillin.

Obviously, this book is not to be recommended as a text-book. As it can be read in a few hours, the perspective it affords will be of great benefit to the student in the early part of his formal instruction in pharmacology.

A. C. B.

The Precentral Motor Cortex. Edited by PAUL C. BUCY. 605 pp. $4.50 paperbound; $5.50 clothbound. The University of Illinois Press, Urbana, Illinois. 1944 (Illinois Monographs in the Medical Sciences, Vol. IV, Nos. 1–4).

This book presents in monographic form a summary of the latest developments of the physiology of the precentral motor region of the cerebral cortex. It brings together in one volume divergent researches by authors who are pre-eminent in the field which they present. The book is dedicated to the memory of Otfrid Foerster, who "stimulated the recent renaissance of interest in the activity of the human cerebral cortex, emphasized the correlation of its physiological activity with the microscopic structure, recognized the importance of animal experimentation for the understanding of human problems, and insisted on the confirmation of the results of animal experimentation by observations on man." In the foreword, Dr. John F. Fulton pays tribute to the late J. G. Dusser de Barenne, whose brilliant program of research led to important additions to the understanding of the precentral region.

The monograph consists of eighteen chapters. Gerhardt von Bonin contributes a chapter giving a lengthy comparative description of the cytoarchitecture of the motor areas in subhuman primates and man. James L. O'Leary studies the relation of cytoarchitecture to electrical activity of the cortex. A. Earl Walker describes afferent connections, Paul M. Levin, efferent fibers, Sarah S. Tower, the pyramidal tract, Warren S. McCulloch, cortico-cortical connections, Margaret A. Kennard, somatic and autonomic functions, and Percival Bailey, relationship to the cerebellum. There is included in this monograph a translation of the excellent though unfamiliar paper by Bubnoff and Heidenhain (1881) on the physiology of the precentral cortex. This paper deals primarily with the electrical excitability

of this region. Wilbur K. Smith has a chapter on the frontal eye fields, Theodore C. Erickson a report on the electrical excitability of the human cortex. The affects of extirpation in man are presented by Paul C. Bucy, who also discusses the relation of the precentral motor cortex to abnormal involuntary movements. Clinical symptomatology of the region is treated by Charles D. Aring, while Charles Davison has contributed the chapter on pathology. The final chapter, by Marion Hines, deals with the significance of the precentral motor cortex. There is an extensive bibliography and index.

This volume represents a summing up of all the important findings to date on the precentral motor cortex. It is therefore valuable for those who would know what has thus far been accomplished and to make available a coherent summary and a guide to the literature.

F. J. O.

Segmental Neuralgia in Painful Syndromes. By BERNARD JUDOVICH and WILLIAM BATES. 313 pp. Illus. $5.00. F. A. Davis Company, Philadelphia, 1944.

The purpose of this monograph is "to show that, clinically, the interpretation of pain can be greatly facilitated by eliciting hyperalgesia or tender skin zones which accompany the pain." When the combination of pain and segmental skin tenderness exists, the cause is more likely to be of somatic than of visceral origin, the disturbance usually involving directly the spinal nerve trunks, roots, or ganglia.

In successive chapters the authors discuss painful syndromes as related to the dermatomes forming the brachial plexus, those supplying the chest and abdomen. Two chapters are devoted to neuralgic aspects of low back pain and sciatica.

All the various etiologic factors in the production of segmental pain and tenderness are enumerated and discussed, greatest being laid upon upper respiratory infections with "toxic absorption," and on postural defects. It is the opinion of the reviewer that too much emphasis is placed on these etiologic factors in which no pathologic studies are available, and too little attention is given to the possible (and no doubt frequent) psychogenic origin of the pain.

Treatment is directed to removal of the cause if it can be found, to infiltration of spinal nerves with novocaine, alcohol, or ammonium sulfate, if no mechanical disturbance is demonstrable. Three chapters are devoted to the technique of nerve infiltration.

Reproductions of X-Rays are excessively poor. The book is considerably less than a major contribution.

F. J. O.

Textbook of Gynecology. By EMIL NOVAK. Second Edition, 708 pp., Illus. $10.00. Williams & Wilkins, Baltimore, 1944.

This is a new edition of the work published in 1941 under the title Gynecology and Female Endocrinology. The general plan followed in the first book has been used in the new one, but many valuable additions have been made. A new chapter

by Houston S. Everett on female urological conditions increases materially, the value of the book to the general practitioner as well as to the woman specialist. A separate chapter on the embryology of the female generative organs will help the medical student to understand this rather complicated subject.

Details of operative technique have been omitted as they were in the first edition. The wisdom of this striking departure from the usual plan of gynecological textbooks was indicated by the favorable comments in the reviews of the first edition. The author's extensive pathological experience and his great interest in the endocrinological conditions encountered in gynecology makes the parts of the book that deal with these subjects especially instructive. The enthusiastic reception given the first edition will surely be extended to this new one. It is an excellent textbook of gynecology, admirably suited to the needs of the student.

L. B.

X-Ray Examination of the Stomach. By FREDERIC E. TEMPLETON. 1st ed 516 pp. Illus. $10.00. University of Chicago Press, Chicago, 1944.

The author presents quite clearly the importance of special knowledge and training in the field of roentgenology of the gastrointestinal tract.

He very properly emphasizes the importance of the fluoroscopic examination and describes in detail the methods employed in the study of the lesion. He stresses the necessity of making "spot films" during the course of the fluoroscopic examination, as that is frequently the only opportunity which is presented for the demonstration of certain pathological conditions.

This book contains an abundance of fine illustrations depicting the majority of lesions which occur in the esophagus, stomach, and duodenum. When possible the author attempts a correlation of the roentgenologic studies with the pathological specimens, gastroscopic observations, laboratory data, and clinical findings.

This volume by a radiologist is a welcome addition to this field of diagnostic roentgenology.

M. McQ-W.

Gastro-Enterology. By HENRY L. BOCKUS. 3 Vols. 2700 pp. $35.00. Saunders, Philadelphia, 1944.

The marked advances in the field of digestive diseases in the past quarter century has necessitated—as the author of these volumes has so well pointed out—the detachment of gastro-enterology from the broad field of internal medicine. Most of this amassed specialized knowledge has been systematically, comprehensively, lucidly and critically recorded in two huge volumes by Henry L. Bockus, one of the leaders in this field. The remaining data will appear in a third volume which is now in preparation.

It is impossible in this brief review to detail so vast a work. Suffice it to say the first volume concerns the esophagus and stomach; the second, the small and large intestines and peritoneum. The third will deal with the liver, gall-bladder,

pancreatic and secondary gastro-intestinal disorders. The first volume was written by Bockus in its entirety. In the second he had the aid of able colleagues and associates—Tumen, Rhoads, Pessel, Johnson, Monaghan, Berk and Banks.

This prodigious effort was completed in the face of wartime burdens, the directing of teaching and investigation as well as in the engaging of active clinical practice. It stands as a challenge to many of us similarly situated.

Of course, errors can be encountered here and there, but these are unimportant; besides, perfection is not for mere mortals. Considered from the standpoint of the whole these volumes constitute a first rate reference work and can be unreservedly recommended. Dr. Bockus should feel proud of his accomplishment. The publishers too should be complimented for they have done their job well.

M. P.

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